Transperineal Saturation Prostate Biopsy

NYU Case of the Month, March 2019

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Our first case is a 69-year-old man who presented in September 2016 with a recent serum prostate-specific antigen (PSA) level of 28.8 ng/mL following institution of exogenous testosterone therapy.

Case 1

Past Medical History

He had a longstanding history of a rising PSA, dating back over 7 years, during which time he underwent five consecutive transrectal ultrasound-guided systematic biopsies demonstrating no cancer. At the time of his fifth biopsy, his PSA rose to 23.4. As it was benign, the patient desired exogenous testosterone and was started on it after being counseled regarding the risk of occult prostate cancer. His PSA rose to 28.8 ng/mL. A 4Kscore® Test (BioReference Laboratories, Elmwood Park, NJ) was performed that suggested a 36% risk of high-grade prostate cancer, and he was referred to NYU Langone Health for further evaluation.

The patient had a motor vehicle accident in the distant past which resulted in chronic back pain following multiple orthopedic procedures. He has a spinal cord stimulator placed for chronic pain approximately 20 years before presentation, precluding the use of magnetic resonance imaging.

Evaluation and Treatment at NYU Langone

Based on his high risk of occult prostate cancer, a repeat biopsy was recommended. Given his multiple previous negative transrectal systematic samplings, a transperineal saturation biopsy was suggested.

On November 1, 2016, a robotic-assisted transperineal saturation biopsy was performed using the iSR'obot™ Mona Lisa device (Biobot Surgical Pte Ltd, Singapore). Thirty-two cores were taken from the right and left according to the Biobot-derived template plan. Pathology demonstrated cancer in 5/32 cores, with Gleason score 4 + 3 cancer demonstrated in the left anterior mid, and small deposits of Gleason 3 + 3 in the surrounding quadrants. In view of his high-risk clinical features (PSA >20 ng/mL), he underwent CT abdomen/pelvis and bone scan revealing no metastatic disease.

After discussion of options, the patient elected to undergo robotic-assisted radical prostatectomy on December 21, 2016. His baseline International Prostate Symptom Score (IPSS) was 9 and Sexual Health Inventory For Men (SHIM) score 8. He was bothered by irritative urinary symptoms. He was not sexually active due to depression but was able to have erections with the use of sildenafil citrate. His surgery was uncomplicated, and he was discharged the morning after surgery.

His pathology demonstrated a dominant 25-mm Gleason 3 + 4 tumor in the left anterior mid gland with focal extracapsular extension and negative surgical margins. There was no cancer identified in 15 removed lymph nodes. His final stage was pT3a, N0. After discussion of options, he elected to defer adjuvant radiotherapy.

At last follow-up in late 2018, his PSA remains undetectable at <0.02 ng/mL. He is totally continent and wears no pads. He remains hypogonadal but has elected not to pursue exogenous testosterone. He has not recovered erections but can achieve orgasm through self-stimulation.

Case 2

Presentation

A 66-year-old man presented with a serum PSA of 5.43 ng/mL in March 2008.

Past Medical History

In July 2008, a transrectal ultrasound–guided prostate biopsy was performed demonstrating Gleason 3 + 3 prostate cancer in <5% of 1/12 cores. He elected active surveillance. In follow-up, his PSA rose to 6.54 ng/mL in September 2008. A repeat, confirmatory 12-core biopsy performed in February 2009 demonstrated no cancer. In follow-up, his PSA remained largely stable until late 2009. A prostate MRI was requested and was read as normal, without regions of suspicion for prostate cancer. A surveillance 12-core systematic biopsy was performed in February 2010, demonstrating high-grade prostatic intraepithelial neoplasia (HGPIN) in 1/12 cores. The patient developed post-biopsy sepsis requiring hospitalization.

Following recovery, he remained on surveillance with a plan for a prolonged interval until the next biopsy. In September 2010, a repeat MRI remained normal, without regions suspicious for prostate cancer. His PSA remained stable until early 2012, but during that time, he underwent hip replacement surgery. In April 2012, a repeat MRI was read as normal but obscured due to artifacts from his hip prosthesis. No biopsy was recommended.

In September 2013, his PSA rose to 9.1 ng/mL. A repeat PSA in February 2014 was 11.22 ng/mL. A repeat MRI demonstrated a focal abnormality but remained obscured by hip prosthesis artifact.

An MRI-targeted biopsy, performed by MRI fusion, demonstrated focal acute inflammation at the site of MRI abnormality, and Gleason grade 3 + 3 prostate cancer in 3/12 systematic cores. His biopsy was again complicated by sepsis, requiring hospitalization.

Following recovery, his PSA continued to rise, initially attributed to residual inflammation from his sepsis event. In December 2014, his PSA rose to 10.4 ng/mL. By May 2016, his PSA rose to 14.2 ng/mL, but he refused biopsy. A repeat MRI was read as Prostate Imaging Reporting & Data System (PI-RADS) 1, with no regions suspicious for prostate cancer. By January 2017, his PSA rose to 16.3 ng/mL. In view of his multiple previous non-informative transrectal samples, along with his concern of recurrent sepsis, a transperineal prostate biopsy was recommended.

Evaluation and Treatment

In March 2017, at age 75, a robotic-assisted transperineal saturation biopsy was performed using the iSR'obot Mona Lisa device. Twenty-three cores were taken from the right and left according to the Biobot-derived template plan demonstrating Gleason 3 + 4 cancer in 1/23 cores from the left anterior mid gland. Based on his intermediate risk features, no further imaging was performed for staging. His baseline IPSS was 9, with minimal bother. His SHIM score was 24 without the use of oral phosphodiesterase type 5 (PDE5) inhibitors, and he reported regular sexual activity. After discussion of options, he elected to undergo treatment with external beam radiotherapy and 6 months concomitant androgen deprivation therapy. He completed 7920 cGy of conventionally fractionated intensity modulated radiation therapy and daily image guidance on August 8, 2017.

At last follow-up in late 2018, his PSA is 0.11 ng/mL with reduced serum testosterone persisting since the cessation of androgen deprivation therapy, to a peak of 194 ng/dL. He has not recovered erections with a reported SHIM score of 0. His IPSS is 7, with mild frequency, but minimal bother.

Discussion

Historical Considerations With Transperineal Biopsy

The role of transperineal saturation biopsy has evolved in recent years of clinical practice, due, in part, to a shifting diagnostic paradigm and a change in the goals of prostate biopsy. In its early application within the transrectal ultrasound era, transperineal saturation biopsy emerged as a tool for improving cancer detection through improved sampling efficiency. During the early 1990s, following the clinical inception of PSA as a diagnostic tool, men frequently underwent multiple biopsies due to an observed relatively high rate of false-negative results on initial sextant biopsies. In the late 1990s, extended systematic template biopsies of 10 to 12 cores emerged as a standard to maximize detection and reduce the need for repetitive prostate biopsy. Despite extending the template, missed cancers

remained a concern, mainly due to the relatively high likelihood of missing cancers within the anterior transition zone when using traditional transrectal sampling. Transperineal template-guided saturation biopsies emerged as a means of maximizing sampling of the gland, inclusive of the anterior transition zone and fibromuscular stroma. Several authors reported high detection rates of up to 45% when using transperineal saturation biopsy in men with previous negative biopsy and persistent clinical suspicion for prostate cancer. Many began to report increasing cancer detection rates with increasing numbers of biopsy cores, not only on repeat biopsy but on first biopsy as well.

As we have learned more about the impact of PSA screening in detection, the urologic community has come to realize that many prostate cancers detected through extensive sampling of the prostate are reflective of occult indolent cancers unlikely related to the PSA elevation and unlikely to cause harm within the natural longevity of the patient. To some extent, this incidental detection of indolent cancer contributes to the dilution of benefits in mortality following population-based screening on a broad scale and contributes to the risk of unnecessary treatment in the individual patient. With acceptance of the observation that it is not desirable to detect all prostate cancers, the definition of an optimal prostate biopsy has evolved as well. In 2013, we contributed to an American Urological Association white paper on the optimal prostate biopsy. In that document, we defined the optimal biopsy as one that allows (1) detection of potentially lethal prostate cancer, (2) avoidance of "over-detection" of clinically insignificant cancer, (3) generation of clinically useful data, and (4) maintenance of cost effectiveness. Achieving these goals requires a balance between adequate sampling and avoidance of oversampling. The white paper ultimately concluded that for most men undergoing biopsy, particularly first biopsy, the optimal number of cores to maximize detection while avoiding over-detection of indolent cancer is 10 to 12. As such, the role of transperineal saturation biopsy in the diagnostic setting would appear to be limited to select situations in which there remains high clinical suspicion despite negative conventional sampling and/or non-informative imaging.

Transperineal Biopsy in the Contemporary Era

In the contemporary area, diagnostic prostate biopsy has been greatly altered by the introduction of prostate MRI. Over the past decade, advances in multiparametric MRI of the prostate have made imaging and localization of prostate cancer feasible in most patients presenting with suspicion of prostate cancer. As such, with the improved accuracy of prostate biopsy and the reduced likelihood of missed occult cancers, the need for diagnostic saturation biopsy has declined.

In Case 1, the patient had a medical contraindication to prostate MRI, and, as such, had been biopsied multiple times by conventional transrectal ultrasound-guided systematic biopsy. His PSA continued to rise and a 4Kscore Test suggested high risk for occult clinically significant cancer. In cases of rising PSA with multiple negative transrectal systematic biopsies, the clinician should have a strong suspicion of an occult transition zone cancer. Transition zone cancers often produce very high levels of PSA without palpable induration, evidence of locally advanced disease, or evidence of metastatic progression. In patients suspected of having cancer missed by conventional transrectal biopsy, transperineal sampling offers a means of sampling regions of the prostate not previously sampled. Furthermore, saturation biopsy ensures adequate sampling of the larger anterior prostate, as well as the apex and extreme base, regions in which cancers are frequently missed by conventional systematic sample. Among men with suspicion of transition zone cancers, anterior saturation can be carried out by transrectal approach, but a transperineal saturation allows far better sampling of the region, extending to the anterior fibromuscular stroma.

In men who can undergo a prostate MRI prior to biopsy but demonstrate no (PI-RADS 1) or low (PI-RADS 2) suspicion, there is great controversy regarding the need for prostate biopsy. In the recently published PRECISION study, deferral of biopsy of men with PI-RADS 1/2 MRI would avoid biopsy in 28% of men presenting with elevated PSA. Studies such as the PROMIS study, however, suggest that MRI misses up to 24% of clinically significant (Gleason score $\geq 3 + 4$) cancers. Our own experience at NYU Langone has suggested that if performing a systematic biopsy, $<10\%$ of men with PI-RADS 1/2 designation are found to have clinically significant cancer. Our experience is consistent with the findings of the recently published MRI-FIRST study in which men with PI-RADS 1/2 MRI demonstrated clinically significant cancer 11% of the time. As such, we have proposed that men with low suspicion MRI may be considered for deferral of biopsy with measurement of PSA velocity over time, or further risk stratification by alternate biomarkers such as 4Kscore Test, to determine the need for biopsy. In men with high suspicion for clinically significant

cancer based on PSA, age, family history, or alternate biomarkers, biopsy should be performed, and transperineal saturation should be considered as a means of minimizing the chance of a false-negative biopsy. This is particularly true of men with a previous negative biopsy.

In Case 2, the patient had undergone multiple biopsies on surveillance suggesting low-grade, small-volume prostate cancer, but his PSA continued to rise, drawing concern for an occult cancer Table 1. The strong suspicion of a missed high-grade cancer was increased by the poor quality of imaging due to artifact from the hip implant, reducing confidence in the imaging findings. In this case too, the clinician should have a strong suspicion for a transition zone cancer given the markedly elevated, rising PSA and multiple non-informative transrectal biopsies. On this basis alone, a transperineal saturation

TABLE 1

Case 2 Clinical History

Date	PSA (ng/mL)	Testosterone (ng/dL)	PCA3	Treatment/ Biopsy	MRI
7/2008	5.43			12-core biopsy: Gleason 6/10, 1 core, <5%	
9/2008	6.54				
2/2009				12-core biopsy: negative	
6/2009	4.8				
12/2009	7.02				
12/2009	4.0		66		MRI normal, no suspicious regions
2/2010				12-core biopsy: negative for cancer; left apex HGPIN, right base HGPIN	
			Biopsy complicated by sepsis		
9/2010	4.3		80		MRI normal, no suspicious regions
3/2011	6.0		143		
10/2011	7.7		56		
4/2012	6.5				MRI normal, hip prosthesis interference
1/8/2013	7.3				
9/9/2013	9.1				
2/13/2014	11.22		367		MRI focally abnormal, but persistent hip prosthesis interference
3/27/2014				12-core biopsy and MRI-targeted biopsy: Gleason grade 3 + 3 = 6 in 3/12 systematic cores; MRI-targeted biopsy negative for malignancy, with focal acute inflammation	

(*Continued*)

		Biopsy complicated by sepsis		
12/3/2014	10.00			
5/5/2015	10.4			PI-RADS 2/5, low suspicion region in right mid gland
12/4/2015	13.2			
3/19/2016	13.5			
5/17/2016	14.2			
6/2/2016				PI-RADS 1, no regions suspicious for cancer
9/15/2016	15.6			
1/28/2017	16.3			
3/7/2017			Gleason 3 + 4 in 1/20	
5/5/2017	16.77			
5/16/2017			Degarelix 240 mg	
6/19/2017	3.22	16	Leuprolide 22.5 mg	
8/18/2017			Last day RT, 7920 cGy	
9/19/2017	0.28	18	Leuprolide 22.5 mg	
12/20/2017	0.04			
3/13/2018	0.03			
5/2/2018		194		
6/12/2018	0.12	142		
12/12/2018	0.11	91		

HGPIN, high-grade prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; PCA3, prostate cancer antigen 3; RT, radiation therapy.

biopsy would be the best option for maximizing the chance of finding high-grade cancer and minimizing the need for future biopsies.

An additional factor to be considered in Case 2 is the history of recurrent post-biopsy sepsis following transrectal biopsy. Although it does not appear that men with previous post-biopsy sepsis episodes would be at higher risk of subsequent sepsis, they are often concerned and reluctant to undergo another transrectal procedure. Furthermore, men at high risk of antibiotic resistance may be considered for transperineal biopsy to minimize the chance of infection. Transperineal sampling has a negligible risk of post-biopsy infection and is growing in popularity for this reason alone in parts of the world where antibiotic resistance is highly prevalent. In the United States, the rate of post-biopsy febrile infection/sepsis continues to rise with several centers reporting rates of 3% to 4% with occasional fatal or near-fatal sepsis events. Antibiotic strategies to reduce infection with transrectal biopsy, including adequate rectal cleansing, use of antibiotics starting within 24 hours prior to the biopsy and extending to 24 hours beyond the biopsy, along with antibiotics tailored to local antibiograms or pre-biopsy rectal swab cultures, have been effective in reducing rates of post-biopsy infection to date. As such, transperineal biopsy has not caught on as a standard biopsy technique for all within the United States, but progressive antibiotic resistance over time may demand such a shift in future practice.

Use of Transperineal Biopsy in Disease Mapping/Improved Sampling of Cancer

With growing interest in focal ablative therapy for prostate cancer, an additional potential use of transperineal saturation biopsy is in the mapping of prostate cancer within the gland. Early focal ablation trials in the pre-MRI era reported the use of transperineal template-guided mapping biopsy as a means of assessing the location and extent of prostate cancer. As many ablative therapies are delivered through placement of transperineal needles

TABLE 2

Indications for Transperineal Saturation Biopsy at NYU Langone Health Urology

Absolute Indications
Repeat biopsy in men unable to undergo prostate MRI (particularly if multiple previous negative biopsies)
Persistent suspicion of prostate cancer in men with low suspicion prostate MRI and previous negative biopsy (may be based upon clinical risk—PSA, PSA velocity, age, family history, alternate biomarkers) History of proctectomy
Relative Indications
History of previous post-biopsy sepsis/infection, or high risk of infection due to known antibiotic-resistance
Persistent suspicion of prostate cancer in men with low suspicion prostate MRI and no previous prostate biopsy (may be based upon high clinical suspicion of transition zone cancer or concern of poor sampling due to large gland)
Planning for transperineal probe/needle based focal ablative therapy
History of proctitis, inflammatory bowel disease, previous rectal surgery, rectal stenosis

PSA, prostate-specific antigen.

or probes (cryosurgery, vascular-targeted photodynamic therapy, laser, radiofrequency, electroporation), there is a belief that transperineal biopsy mapping may provide a more intuitive treatment map, well aligned with the therapeutic application. Additionally, transperineal saturation may identify secondary, tertiary, and quaternary sites of disease, not identified on MRI or conventional biopsy, that might be treated due to the knowledge of spatial location. At NYU Langone, we have generally employed a technique of image-guided (MRI) focal ablative therapy, and, as such, have not routinely employed transperineal saturation biopsy techniques in focal therapy planning Table 2. ■